

## Original Article

## Incidence and timing of biphasic anaphylactic reactions: a retrospective cohort study

Motohiro Ichikawa,<sup>ID</sup> Akira Kuriyama,<sup>ID</sup> Seigo Urushidani,<sup>ID</sup> and Tetsunori Ikegami

Emergency and Critical Care Center, Kurashiki Central Hospital, Okayama, Japan

**Aim:** We investigated the frequency of overall biphasic reactions, biphasic reactions that met the diagnostic criteria of anaphylaxis, and biphasic reactions that caused a severe abnormality in vital signs in patients who visited the emergency department of a tertiary hospital.

**Methods:** This retrospective cohort study included patients aged 18 years or over who presented with anaphylaxis at the emergency department of a tertiary care hospital between January 2014 and December 2016. The primary outcome was the incidence of biphasic reactions that caused a severe abnormality in vital signs and developed within 7 days. Secondary outcomes were the frequency of overall biphasic reactions and those that met the diagnostic criteria of anaphylaxis.

**Results:** In total, 437 patients aged over 18 years visited the emergency department during the study period. Among them, 202 were enrolled in this study. The proportion of patients who had overall biphasic reactions, those that met the diagnostic criteria of anaphylaxis, and those with a severe abnormality in vital signs was 8.9%, 3.0%, and 1.0%, respectively. Overall, 32.7% of patients were hospitalized, but hospitalization aided in the treatment of severe biphasic reactions at the early stage in only one patient.

**Conclusion:** We found that 8.9% of adult patients with anaphylaxis had a biphasic reaction, but biphasic reactions together with severe abnormalities in vital signs were rare.

**Key words:** Anaphylaxis, antigen–antibody reaction, hypersensitivity, observation, shock

## BACKGROUND

ANAPHYLAXIS CAN BE fatal due to respiratory deterioration or cardiac arrest; therefore, initial treatment significantly affects patient prognosis. Most anaphylaxis patients show rapid improvement with drugs such as epinephrine. However, there is a risk of biphasic reactions; hence, close observation for a certain period is recommended.<sup>1</sup> International guidelines published in 2020 recommend 1-h observation for mild cases and 6-h observation for severe cases.<sup>2</sup>

However, some biphasic reactions can reportedly develop 24 h or later after the first anaphylaxis attack. The reported frequency of biphasic reactions ranges from 1.4%

to 20%,<sup>3–6</sup> which could be due to the variation in the characteristics of patients, definition of biphasic reaction, and duration of observation.<sup>1,7–9</sup> Some previous studies have not defined biphasic reaction clearly, and the frequency reported in these studies could be for mild cases, such as urticaria. Other studies have defined biphasic reaction as symptoms that meet the diagnostic criteria for anaphylaxis according to international guidelines. However, mild dermal and respiratory symptoms also meet the criteria. The frequency of biphasic reaction reported in these studies might also include reactions that do not require hospitalization. The information required by physicians who treat anaphylaxis is the frequency of severe biphasic reactions that could lead to delay of care unless under hospitalized observation. Therefore, our main focus was on the frequency of biphasic reactions that cause severe abnormalities in vital signs.

In this study, we aimed to investigate the frequency and time to onset of overall biphasic anaphylactic reactions, those that meet the criteria for anaphylaxis, and those with severe abnormalities in vital signs at the emergency department (ED) of a tertiary hospital.

**Corresponding:** Motohiro Ichikawa, MD, Emergency and Critical Care Center, Kurashiki Central Hospital, 1-1-1 Miwa Kurashiki, Okayama 710-8602, Japan. E-mail: motohiro-i@sannet.ne.jp.

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## METHODS

### Study design and setting

**T**HIS single-center retrospective observational study was undertaken at Kurashiki Central Hospital, a tertiary hospital located in the southwestern area of Okayama prefecture, where 65,000 patients visit the ED annually. This research was approved by the institutional review board of Kurashiki Central Hospital.

### Participants

In our ED, all patients are diagnosed by the treating physicians, and their data is electronically recorded in the register according to the International Classification of Diseases-10 code. We extracted the data of patients aged 18 years or older with diagnosis reported as anaphylaxis in the register from January 1, 2014 to December 31, 2016. We also screened for patients who were hospitalized from the ED during the study period and extracted the details of all patients registered under the disease name “anaphylaxis”. We examined the extracted records and selected patients based on the following inclusion criteria: (i) patients who satisfied the diagnostic criteria of the World Allergy Organization published in 2011 (Table 1),<sup>10</sup> (ii) patients whose symptoms were confirmed to be caused by allergies. We excluded patients based on the following exclusion criteria: (i) patients who did not meet the World Allergy Organization criteria, (ii) patients whose symptoms were due to other diseases, (iii) patients whose reason for the first visit to the hospital in the study period was a biphasic reaction.

We also excluded patients aged less than 18 years for the following reasons: (i) these patients often lacked vital signs in their medical charts, (ii) many of them were followed up in other hospitals and it was difficult for us to obtain details of the incidence of the biphasic reactions.

### Measurement

We investigated the medical records of all the included patients for 7 days after they visited the ED with anaphylaxis. We extracted data about the age, sex, anticipated antigen, treatment, and disposition of the patients at the ED by reviewing their medical records. We also gathered information regarding the use of epinephrine, corticosteroids, histamine 1 (H1) antagonist, histamine 2 (H2) antagonist, and intubation in the ED. In addition, we noted their discharge information from the ED (discharge to home or admission to the general ward or intensive care units [ICUs]) and duration of follow-up by inpatient or outpatient management. We

**Table 1.** Diagnostic criteria of anaphylaxis from the clinical practice guidelines published by the World Allergy Organization in 2011

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both and at least one of the following conditions:
  - a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia, collapse, syncope, incontinence)
2. Two or more the following that occur rapidly after exposure to a likely allergen for that patient:
  - a. Involvement of the skin-mucosal tissue
  - b. Respiratory compromise
  - c. Reduced BP or associated symptoms
  - d. Persistent gastrointestinal symptoms
3. Reduced BP after exposure to known allergen for that patient
  - a. Infant and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
  - b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Abbreviations: BP, blood pressure; PEF, peak expiratory flow.

investigated the frequency of overall biphasic reaction, those that met the criteria for anaphylaxis (Table 1), and those with a severe abnormality in vital signs within 7 days of the ED visit. We defined a biphasic reaction when a patient had symptoms in any of the four organ systems (skin-mucosal tissue, respiratory system, circulatory system, and gastrointestinal system) described in the criteria of the anaphylaxis guidelines mentioned above without any new antigen exposure after resolution of the first anaphylaxis attack symptoms.<sup>10</sup> We defined biphasic reactions with severe abnormalities in vital signs as biphasic reactions with systolic blood pressure less than 80 mmHg, heart rate greater than 120 b.p.m., or oxygen saturation less than 90%. In previous studies, the mean age of anaphylaxis patients was between 20 and 40 years, which was younger than that observed for other medical diseases.<sup>4–6</sup> Although the above guidelines showed a systolic blood pressure of less than 90 mmHg as one of the definitions of anaphylaxis,<sup>10</sup> the official statistical data of the Japanese government in 2019 showed that 24.6% of women aged in their 20s have a systolic blood pressure of less than 100 mmHg at normal times.<sup>11</sup> Thus, we defined a systolic blood pressure of less

than 80 mmHg as a severe vital sign abnormality in our study. Tachycardia is usually defined as a heart rate of 100 b.p.m. or higher. However, we believe that higher numerical values are necessary for defining severe vital sign abnormalities. Previous reports have shown a heart rate of 120 b.p.m. as one of the stabilization goals for critically ill patients.<sup>12</sup> Therefore, we defined a heart rate of 120 b.p.m. or higher as a severe vital sign abnormality. We also defined oxygen saturation of less than 90% as a severe vital sign abnormality concerning respiratory conditions according to a guideline for oxygen therapy for acutely ill medical patients.<sup>13</sup>

In patients with any biphasic reaction, we investigated age, sex, treatment for the first attack, time from the first attack to biphasic reaction, type of biphasic reaction, and treatment for the biphasic reaction. Furthermore, we investigated the setting in which the biphasic reaction occurred (at the ED or hospital ward, or after discharge to home).

We also present a brief summary on patients who had a biphasic reaction with a severe abnormality in vital signs.

Additionally, we investigated the cases wherein patients were followed up for 3 days or more. We included patients who visited the outpatient ward on 3 days or more after the initial attack and those who were admitted for more than 3 days. We extracted the data of these patients and analyzed the incidence of biphasic reactions in them as well.

## Measured outcomes

The primary outcome of this study was the incidence of biphasic anaphylactic reactions with a severe abnormality in vital signs within 7 days of the first anaphylactic attack. The secondary outcomes were the frequency of overall biphasic reactions and the frequency of biphasic reactions that met the criteria for anaphylaxis.

## Statistical analysis

We compared the age of patients with and without a biphasic reaction using the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. We used a two-sided test, and  $P < 0.05$  indicated statistical significance. We used EZR for statistical analysis.<sup>14</sup>

## RESULTS

### Baseline characteristics

**D**URING THE STUDY period, 437 patients aged 18 years or older visited the ED for anaphylaxis. We excluded 199 patients who did not meet the criteria for

anaphylaxis, 30 patients who were diagnosed with diseases other than anaphylaxis, and six patients whose reason for the first visit was a biphasic reaction. Eventually, 202 patients were included in this study. Among them, 136 were discharged from the ED and 66 were hospitalized, 11 of whom were admitted to the ICU (Fig. 1). The median duration of hospitalization for all hospitalized patients was 2 days.

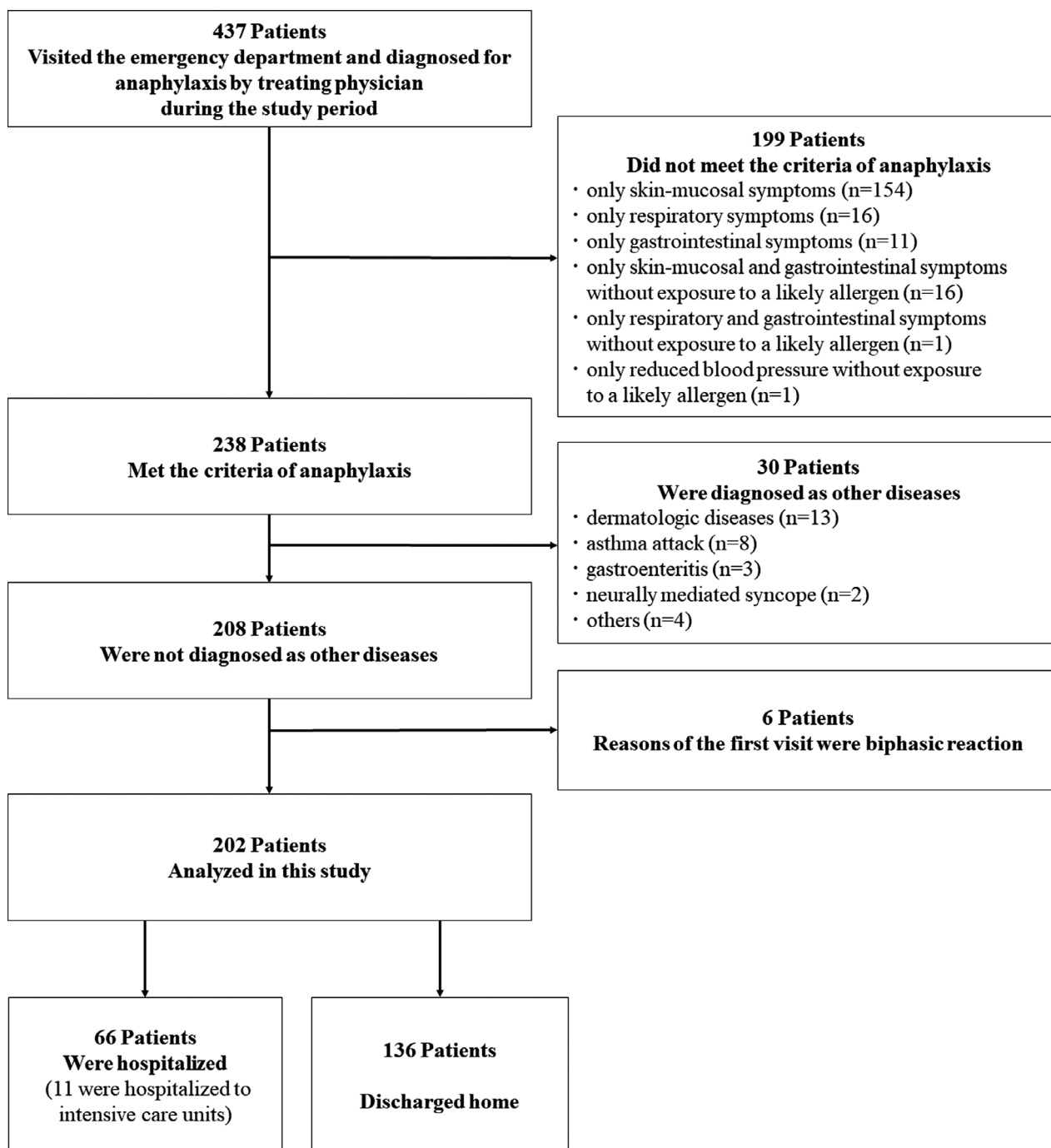
Among the 202 patients included in this study, the median patient age was 46 years, and 48 patients (23.8%) were aged 65 years or older. Ninety-three patients (46.0%) were men. The most prevalent antigens were those from food, followed by drugs, and the most common treatment was H1 antagonists. Sixty-four patients (31.7%) were followed up for 3 days or more by outpatient or inpatient management. Fifty-five patients (27.2%) were followed up for 1–2 days and 83 (41.1%) were followed up for less than 24 h (Table 2), 69 (83.1%) for less than 6 h and two (2.4%) for more than 12 h. The median follow-up periods of patients who were hospitalized and discharged from the ED were 3.5 days and 6.5 h, respectively.

### Biphasic reactions

Overall, 18 (8.9%) of 202 patients included in this study had biphasic reactions. The median age of patients with and without biphasic reactions were 38 and 46 years, respectively. Although not significant, young female patients tended to develop biphasic reactions. Epinephrine tended to be used in the group that developed a biphasic reaction, but there was no significant difference ( $P = 0.131$ ).

Only two (1.0%) of 202 patients had biphasic reactions with severe vital sign abnormalities within 7 days of their first ED visit. Additionally, six (3.0%) had biphasic reactions that met the criteria for anaphylaxis (Table 3). Figure 2 shows the Kaplan–Meier curves of the time until the overall biphasic reactions, biphasic reactions that met the criteria for anaphylaxis, and biphasic reactions with severe abnormalities in vital signs.

Table 4 shows details of the patients who had a biphasic reaction. Among 18 patients who had biphasic reactions, 10 (55.6%) developed biphasic reactions after discharge from the ED: seven patients (38.9%) in the hospital ward and three (16.7%) in the ED. Fourteen (77.8%) and seven patients (38.9%) developed a biphasic reaction within 8 and 12 h, respectively. Most patients had skin or mucosal symptoms (83.3%), followed by respiratory symptoms (27.8%), and six patients (33.3%) had symptoms involving two or more organ systems. Regarding the treatment for biphasic reaction, the proportion of patients who received epinephrine, corticosteroids, H1 antagonist, and H2 antagonist was 27.8%, 44.4%, 55.6%, and 55.6%, respectively.



**Fig. 1.** Flowchart of the study participant selection process.

Table 5 shows the details of the cases who had biphasic reactions with severe abnormalities in vital signs. Case 1 was a 33-year-old woman who visited the ED with a complaint of skin rash that developed after eating citrus; she had hypotension. After initial treatment her symptoms resolved

and she was discharged home. However, she presented with the same symptoms after 3 days. Her symptoms quickly resolved after treatment, and she was discharged from the ED. Case 2 was a 47-year-old man who visited the ED for dyspnea and hypotension after receiving intravenous

**Table 2.** Characteristics of patients with anaphylaxis, grouped according to the incidence of a biphasic reaction

Variable	All patients (N = 202)	Patients with any biphasic reaction (n = 18)	Patients without any biphasic reaction (n = 184)	P-value
Age, years	46 (30–64)	38 (27–56)	46 (30–64)	0.24 <sup>a</sup>
65 years or older	48 (23.8)	3 (16.7)	45 (24.5)	0.57 <sup>a</sup>
Male sex	93 (46.0)	6 (33.3)	87 (47.3)	0.33 <sup>b</sup>
Type of antigen				
Food	83 (41.1)	7 (38.9)	76 (41.3)	0.86 <sup>b</sup>
Drug	57 (28.2)	6 (33.3)	51 (27.7)	
Insect	12 (5.9)	0 (0.0)	12 (6.5)	
Animal	3 (1.5)	0 (0.0)	3 (1.6)	
Unknown	47 (23.3)	5 (27.8)	42 (22.8)	
Treatment at the emergency department <sup>c</sup>				
Epinephrine	121 (59.9)	14 (77.8)	107 (58.2)	0.131 <sup>b</sup>
Corticosteroid	156 (77.2)	15 (83.3)	141 (76.6)	0.77 <sup>b</sup>
Histamine 1 antagonist	187 (92.6)	17 (94.4)	170 (92.4)	1.00 <sup>b</sup>
Histamine 2 antagonist	176 (87.1)	16 (88.9)	160 (87.0)	1.00 <sup>b</sup>
Intubation <sup>d</sup>	4 (2.0)	1 (5.6)	3 (1.6)	0.31 <sup>b</sup>
Disposition as of emergency department discharge				
Discharge to home	136 (67.3)	9 (50.0)	127 (69.0)	0.146 <sup>b</sup>
Admission to general ward	55 (27.2)	7 (38.9)	48 (26.1)	
Admission to intensive care unit	11 (5.4)	2 (11.1)	9 (4.9)	
Duration of follow-up, days				
0 <sup>e</sup>	83 (41.1)	0 (0.0)	83 (45.1)	<0.001 <sup>b</sup>
1–2	55 (27.2)	5 (27.8)	50 (27.2)	
3–6	17 (8.4)	5 (27.8)	12 (6.5)	
7 or more	47 (23.3)	8 (44.4)	39 (21.2)	

Data are shown as median (interquartile range) or n (%).

<sup>a</sup>Calculated by Mann–Whitney *U*-test.

<sup>b</sup>Calculated by Fisher's exact test.

<sup>c</sup>Including treatments at the referral hospital or in the ambulance.

<sup>d</sup>Including cricothyroidotomy.

<sup>e</sup>Cases who were followed up <24 h.

**Table 3.** Frequency of biphasic reaction among patients with anaphylaxis (N = 202)

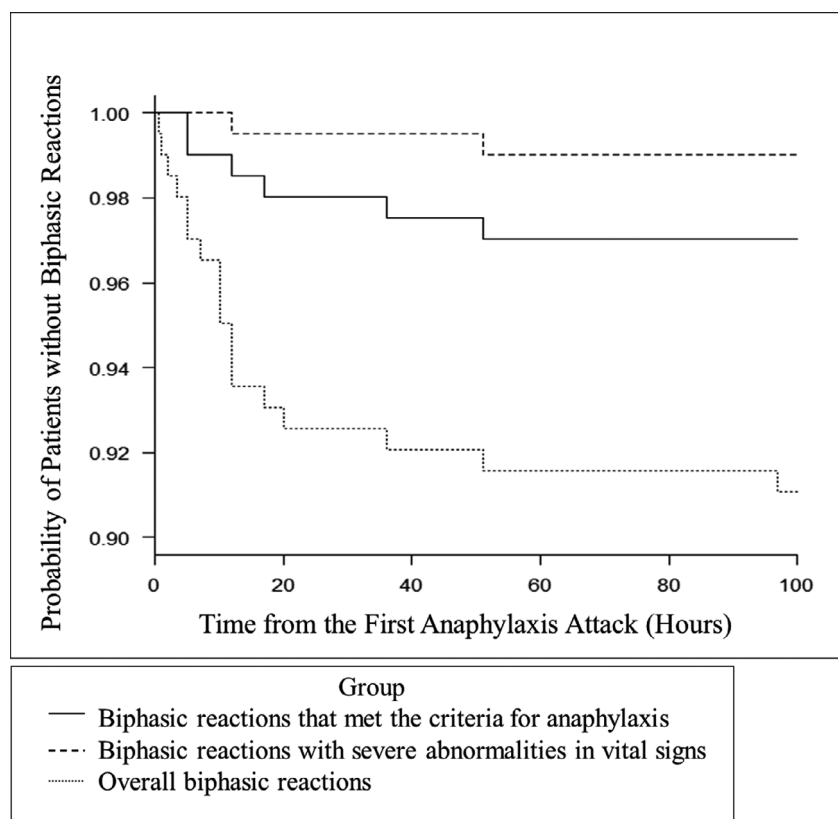
Type of biphasic reaction	n (%)
Any biphasic reaction	18 (8.9)
Biphasic reaction with severe vital sign abnormality <sup>a</sup>	2 (1.0)
Biphasic reaction that met the diagnostic criteria of anaphylaxis from the clinical practice guidelines published by the World Allergy Organization in 2011	6 (3.0)

<sup>a</sup>Defined as a biphasic reaction with systolic blood pressure <80 mmHg, heart rate >120 b.p.m., or oxygen saturation <90%.

antibiotics. His symptoms resolved after initial treatment, and he was hospitalized in the general ward. However, he developed hypotension again after being shifted to the general ward. Subsequently, he needed mechanical ventilation and catecholamine in the ICU. This was the only case wherein hospitalization made it feasible to provide treatment for severe biphasic reactions at an early stage.

### Follow-up of cases for 3 days or more

Sixty-four patients were followed up for 3 days or more (Table 6). Among these 64 patients, the median age was 51 years, and 29 patients (45.3%) were discharged from the ED. The median follow-up period of these patients was 11.5 days. Overall biphasic reactions, biphasic reactions



**Fig. 2.** Biphasic reaction among patients with anaphylaxis ( $N = 202$ ). Kaplan–Meier curves of the time until biphasic reactions, biphasic reactions that met the criteria for anaphylaxis, and biphasic reactions with severe abnormalities in vital signs. Probabilities of patients without biphasic reactions were calculated with all the included patients in this study as the denominator.

with a severe abnormality in vital signs, and biphasic reactions that met the criteria for anaphylaxis were seen in 13 (20.3%), 2 (3.1%), and 6 (9.4%) patients, respectively.

## DISCUSSION

OUR STUDY SUGGESTED that 8.9% of patients who experienced the first episode of anaphylaxis subsequently developed a biphasic reaction. Biphasic reactions that met the criteria for anaphylaxis were seen in 3.0%, and those with a severe abnormality in vital signs were seen in 1.0% of patients.

The frequency of biphasic reactions reported in most previous studies was 4%–6%,<sup>3,5,15</sup> ranging from 1.4% to 20%.<sup>1</sup> In contrast, 8.9% of our patients developed a biphasic reaction, a rate that was slightly higher than those reported in previous studies. In Japan, Oya *et al.*<sup>6</sup> and Ikeda *et al.*<sup>16</sup> reported that the frequency of biphasic anaphylactic reactions in patients who needed hospitalization was 6.1% and 5.9%, respectively. Most previous studies used an

observation period of 72 h, whereas our study defined a biphasic reaction as any anaphylaxis symptom occurring within 7 days of the first anaphylaxis attack. Although the observation period in our study was longer, only one case of biphasic reaction occurred after more than 72 h from the first attack.

There were only two cases of biphasic reactions accompanied by a severe abnormality in vital signs. One of these biphasic reactions occurred after discharge; therefore, there was only one case wherein immediate treatment was provided because of hospitalization. Recommendations regarding the observation period required for detecting biphasic reactions vary across studies. Some studies reported that most cases can be identified by observing patients for 6 or 8 h,<sup>9,17</sup> whereas other studies suggest an observation period longer than 10 h.<sup>3</sup> The guidelines published in 2020 recommend 1-h observation for mild cases and 6-h observation for severe or high-risk cases.<sup>2</sup> In our study, a biphasic reaction developed in only 33.3% cases within 6 h, which suggests that 6-h observation is not



**Table 4.** Details of biphasic reaction among patients with anaphylaxis ( $n = 18$ )

Timing of the development of biphasic reaction <sup>a</sup>	$n$ (%)
After discharge from hospital	10 (55.6)
During hospitalization	7 (38.9)
During observation at emergency department	3 (16.7)
Time between remission of first attack and biphasic reaction	
0–12 h	14 (77.8)
12–24 h	2 (11.1)
24–48 h	1 (5.6)
More than 48 h	1 (5.6)
Organ systems involved in biphasic reaction <sup>a</sup>	
Skin or mucosal symptom	15 (83.3)
Cardiovascular symptom	1 (5.6)
Respiratory symptom	5 (27.8)
Gastrointestinal symptom	2 (11.1)
Biphasic reaction across two or more organ systems	6 (33.3)
Treatment for biphasic reaction	
Epinephrine	5 (27.8)
Corticosteroid	8 (44.4)
Histamine 1 antagonist	10 (55.6)
Histamine 2 antagonist	10 (55.6)
Intubation <sup>b</sup>	1 (5.6)

<sup>a</sup>There are duplications because some cases had multiple biphasic reactions.

<sup>b</sup>Including cricothyroidotomy.

sufficient to screen for biphasic reactions. Although 9 of 12 patients who had a biphasic reaction after 6 h developed it after discharge and returned to the ED, none of them needed hospitalization. All these biphasic reactions seemed mild. Nine of 66 patients (13.6%) who required hospitalization experienced some biphasic reaction, and seven (10.6%) developed the reaction during hospitalization. However, there was only one case of a biphasic reaction that met the criteria for anaphylaxis, and it occurred in the hospital ward. In some cases, hospitalization made it feasible to treat the mild biphasic reactions at an early stage. These mild biphasic reactions might have become severe if the patients were not hospitalized and treated at an early stage. However, for patients who were discharged from the ED, there were no complications due to this management. Therefore, some patients can be followed up safely as outpatients provided they have a reliable observation plan.

This study has some limitations. First, some patients might have had a biphasic reaction after returning home, and they may have visited another hospital or may not have visited any hospital because the reaction was mild.

**Table 5.** Details of two cases of anaphylaxis with a biphasic reaction and severe vital sign abnormality<sup>a</sup>

Case 1	33-year-old woman	The woman visited the emergency department (ED) with a complaint of skin rash that developed after eating citrus; she had hypotension with systolic blood pressure 73 mmHg, and she was diagnosed with anaphylactic shock. After initial treatment with epinephrine, fluid resuscitation, corticosteroids, and histamine 1 (H1) and H2 antagonists, her symptoms resolved and she was discharged home. Three days after the first attack, she visited our ED with a skin rash again. She did not eat citrus at this time. Her systolic blood pressure was 73 mmHg, her heart rate was 101 b.p.m., and her SpO <sub>2</sub> was 99%. Her symptoms quickly resolved again after treatment with epinephrine, fluid resuscitation, corticosteroids, and H1 and H2 antagonists. She was discharged home and did not revisit the ED.
Case 2	47-year-old man	After receiving intravenous antibiotics for cervical lymphadenitis, the patient had a skin rash, dyspnea, and hypotension with a systolic blood pressure of 77 mmHg. His symptoms recovered after initial treatments with epinephrine, fluid resuscitation, H1 and H2 antagonists, and corticosteroids. After initial treatment, he was hospitalized in the general ward. Twelve hours later, he developed dyspnea, hypoxemia with SpO <sub>2</sub> 89%, and skin rash again. His systolic blood pressure was 84 mmHg and his heart rate was 92 b.p.m. Despite the treatment with epinephrine, fluid resuscitation, corticosteroids, and H1 and H2 antagonists, his hypoxemia persisted. He was transferred to the intensive care unit, treated with corticosteroids for 1 day, and needed intensive care with mechanical ventilation and catecholamine for 3 days.

<sup>a</sup>Defined as a biphasic reaction with systolic blood pressure <80 mmHg, heart rate >120 b.p.m., or oxygen saturation <90%.

**Table 6.** Patients with anaphylaxis and biphasic reaction who were followed up 3 or more days (*N* = 64)

Variable	
Age, years	51 (33–70)
65 years or older	21 (32.8)
Male, <i>n</i> (%)	31 (48.4)
Disposition as of emergency department discharge	
Discharge to home	29 (45.3)
Admission to general ward	25 (39.1)
Admission to intensive care unit	10 (15.6)
Any biphasic reaction	13 (20.3)
Biphasic reaction with severe vital sign abnormality <sup>a</sup>	2 (3.1)
Biphasic reaction that met the diagnostic criteria of anaphylaxis from the clinical practice guidelines published by the World Allergy Organization in 2011	6 (9.4)

Data are shown as median (interquartile range) or *n* (%).

<sup>a</sup>Defined as a biphasic reaction with systolic blood pressure <80 mmHg, heart rate >120 b.p.m., or oxygen saturation <90%.

Consequently, they could not be included in this study. The same reason applies to patients who were hospitalized and had a biphasic reaction after discharge. As shown in Table 6, we undertook an analysis on only those patients who were followed up for 3 days or more with an intent to reduce this limitation. The frequency of biphasic reactions was higher in patients who were followed up for 3 days or more than in patients who were followed up for less than 3 days. However, there could be some bias because these data are limited to patients who were selected for a follow-up of 3 days or more by the physician. Moreover, these results might not reflect accurate data of all anaphylaxis patients because they might have been limited to patients with severe reaction or with a risk of biphasic reaction. Second, because our setting is a community-based hospital, patients who had a severe biphasic reaction were more likely to visit our hospital. Patients who had mild biphasic reactions may not be included in this study. Finally, because this is a retrospective study, it is possible that the doctors did not accurately describe the biphasic reactions in the medical records; therefore, the frequency of biphasic reactions might have been underestimated.

Despite these limitations, no previous studies have focused on biphasic anaphylaxis reactions with severe abnormalities in vital signs and reported their frequency. Therefore, this study is the first to focus on these aspects and is clinically relevant.

## CONCLUSION

IN OUR HOSPITAL, the frequency of overall biphasic reactions was 8.9%, that of biphasic reactions that met the criteria for anaphylaxis was 3.0%, and that of biphasic reactions with severe abnormalities in vital signs was 1.0%. Among the anaphylaxis patients who needed hospitalization, only 1.5% were urgently treated for a severe abnormality in vital signs during hospitalization. Although there is scope for discussion about the indications for hospitalization in anaphylaxis patients after their symptoms have resolved completely, follow-up as outpatients could be a safe and feasible choice for patients with a satisfactory observation plan.

## DISCLOSURE

Approval of the research protocol: This research was approved by the institutional review board of Kurashiki Central Hospital (approval no. 2979), and it conforms to the provisions of the Declaration of Helsinki.

Informed consent: The need for informed consent was waived because of the retrospective design of the study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

## DATA AVAILABILITY STATEMENT

THE DATA THAT support the findings of this study are available from the corresponding author upon reasonable request.

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